REMARKS

Reconsideration of this application is requested in view of the amendments to the claims and remarks presented herein.

Applicants' attorney wishes to thank the Examiner in charge of the application for the courtesies extended to him at the interview on November 8, 2001.

The claims in the application are claims 17 to 48, all other claims having been cancelled. Claims 29 to 40 and 48 stand withdrawn as non-elected invention.

All of the claims were rejected under 35 USC 103 as being obvious over the Celeste et al patent taken in view of the secondary and tertiary references. The Examiner was of the opinion that Celeste et al taught mature MP52 containing the amino acid sequence of Celeste et al SEQ ID No: 4 which amino acids 2 to 120 were identical to Applicants' SEQ ID No: 1. The Examiner further states that Celeste et al teaches that the first cysteine of the seven cysteine domain of MP52 is encoded by the codon beginning at nucleotide #899 of Celeste et al SEQ ID No: 3 and the Examiner suggests that SEQ ID No: 4 of Celeste et al would be expected to retain the activity that Applicants have. The Examiner further stated that Applicants' arguments were not deemed to be germane to the rejection and that while the process may be novel or unobvious,

the claims were not limited to a novel or unobvious process and that there was no evidence on record that the shortened form of MP52 would have been expected to have a reduced biological activity and that Neidhardt teaches that MP52 has a pharmaceutical use and the shortened form would have been expected to have activity.

Applicants respectfully traverse these grounds of rejection since the Celeste et al patent taken in view of the secondary art, which the Examiner has combined with the benefit of Applicants' disclosure, would not teach Applicants' invention to one skilled in the art. With respect to the Examiner's contention that he cannot find an example wherein MP52 shows no activity in the cartilage/bone region, Applicants wish to call the Examiner's attention to Example 6 wherein it is indicated that MP52 shows similar results as BMP-12. In Example 6, it states "All proteins showed comparable results similar to those described above for human BMP-12." In Example 5, it is indicated that "For all doses of BMP-12 tested, no bone or cartilage formation was observed in the implants after 10 days." This is a clear teaching that MP52 protein does not possess cartilage or bone formation. Celeste et al teaches that the MP52 reacts as BMP-12 and shows no cartilage or bone formation which is a delimitation against other BMPs with usual cartilage and bone formation. Therefore, the Celeste et al statements on the activity of shortened forms can at best be mere speculation at least concerning the cartilage and bone region. No where is there any example that these forms are actually active and

therefore, Applicants' arguments with respect to the last rejection are clearly supported by the reference.

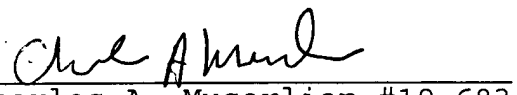
While Celeste et al talks about "expected activity", there is no pertinent showing thereof. In the case of Pro MP52 compared with Ala-Pro-MP52, one can only speculate as to whether the identical activity can be furnished and it can only be shown by pratical experiments. Celeste et al does not show any practical experiments concerning the shortened forms and only defines MP52 activity in the tendon/ligament area and contends that the MP52 does not show any cartilage/bone inducing activity as noted above. The statements with respect to MP52 activity in Celeste et al are at best cannot be applied to activities in the cartilage/bone area because according to Celeste et al, MP52 has no activity in this area. Therefore, there is no teaching of Applicants' method nor is there any clear teaching as to what can be changed in the N-terminus region to define comparable cartilage/bone inducing activity of MP52. The combination with the secondary and tertiary references would not point out Applicants' invention to one skilled in the art. The Ben-Bassat et al reference teaches cleavage of methionine by MAP was tested in vivo by expression of the genes encoding the recombinant MAP hyper-producing E.coli strains. It should be noted that a small fraction of the recombinant proteins after being exposed to MAP either in vitro or in vivo still retained their terminal methionine as can be seen from Table 1 on page 755. Ben-Bassat et al teaches that MAP hyper-producing

strains E.coli provide à mixture of Met-Ala-Pro-IL2, Ala-Pro-IL2 and Pro-IL2. The Tonouchi et al reference teaches "As this fused protein had a Phe-Arg-Ala sequence at the junction of IL-2 and BSF-2, it was possible to process mature BSF-2 from fused BSF-2 by treatment with kallikrein and aminopeptidase." The reference also teaches "After digestion by kallikrein, the N-terminal alanine was removed by E.coli aminopeptidase P which recognizes X-Pro at the N-terminus and digests it before the proline residue." as noted on page 32. Clearly, Tonouchi et al does not concern direct expression of recombinant protein and only discloses in vitro cleavage of X-Pro-N-terminus by the specific peptidase P.

Sherman et al merely teaches "Studies have directly demonstrated that methionine is partially retained on proteins that are actually over produced in E.coli." as noted on page 29. The Georgiou et al reference deals with the presence of the first methionine whose removal is desirable and recombinant proteins that are over produced in E.coli (see page 1240). In other words, one skilled in the art would not combine the secondary and tertiary references as the Examiner has done with the benefit of Applicants' teachings and would not end up with Applicants' novel peptide and the use thereof. Therefore, withdrawal of these grounds of rejection is requested.

In view of the amendments to the claims and the above remarks, it is believed that the claims clearly point out Applicants' patentable contribution and favorable reconsideration of the application is requested.

Respectfully submitted,
Bierman, Muserlian and Lucas

By: 

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CAM:ds
Enclosures

146.1275

MARKED UP COPY OF CLAIMS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: : D. Romeo
F. MAKISHMINA et al :
Serial No.: 945,459 : Group: 1646
Filed: October 20, 1997 :
For: NOVEL PROTEIN...THE SAME :

600 Third Avenue
New York, N.Y. 10016
April 18, 2001

AMENDMENT

Asst.Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend this application as follows:

IN THE CLAIMS:

Cancel all the claims and add the following claims:

--17. An isolated protein consisting of the 119 amino acids as shown in SEQ ID No: 1 ~~without~~ free of ~~residual~~ proteins ~~consisting~~ of ~~the amino acid sequence as shown in~~ SEQ ID No: 1, ~~the said protein~~ with an ~~additional~~ Ala ~~(120 amino acids) and the said protein with~~ OR Met and Ala ~~(121 amino acids)~~ at the N-terminus.

18. An isolated protein according to claim 17 wherein said protein is a homodimer.

19. A pharmaceutical composition comprising the protein of claim 18 and a pharmaceutical carrier.

20. ~~The~~ A pharmaceutical composition ~~of claim 19~~ comprising an amount of the protein of claim 18 effective to treat cartilage and/or bone diseases/and a pharmaceutical carrier

diseases are radicular or alveolar defects.

40. The method of claim 34 wherein said cartilage and/or bone diseases are congenital.

41. A pharmaceutical composition of claim 19 for systemic or local administration.

42. A pharmaceutical composition of claim ~~41~~ 20 as an injectable preparation.

43. A pharmaceutical composition of claim ~~19~~ 20 in the form of an injectable powder.

44. A pharmaceutical composition of claim 20 for coating onto the surface of cartilage, bone or tooth.

45. A pharmaceutical composition of claim 20 ~~for~~ comprising cartilage or bone grafting using natural or artificial bone.

46. A pharmaceutical composition of claim 45 wherein artificial bone means metal, ceramics, glass, collagen and/or hydroxyapatite.

47. The pharmaceutical composition according to claim ~~26~~ 28, wherein the disease is chondrodysplasia, chondrohypoplasia, achondrogenesis, palatoschisis and osteodysplasia.

48. The method of claim ~~38~~ 34 wherein said cartilage and/or bone diseases are chondrodysplasia, chondrohypoplasia, achondrogenesis, palatoschisis and osteodysplasia.--

REMARKS

Reconsideration of this application is requested in view of